REMARKS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

Claims 47-60 are pending in the present application. Claims 42-58 have been amended to recite a method for the treatment of unipolar depression or depression-related disorders, or the prevention of unipolar depression in a person suffering from psychosis, disturbance of personality, loss of a relative, hormonal changes, and neurological disorders. Claims 42-58 have also been amended to correct several informalities found within the claims. New claims 59 and 60 have been added and are directed to a method for the treatment of depression or depression-related disorders in a person suffering from or at risk of suffering from said depression or depression-related disorders. Support for new claims 59 and 60 may be found in claim 42 and in the present specification at page 6, line 9 to page 7, line 17.

In the outstanding Official Action, claims 42-56 and 58 were rejected under 35 USC §112, first paragraph, as allegedly failing to comply with the written description requirement. This rejection is traversed.

In imposing the rejection, the Official Action stated that claims 42, 49, and 55 recite a ratio of 0.5-20:1, 5-12:1 and

2.5-5.5:1, respectively and alleged that these ratios were not described in the specification as originally filed. However, the ratios of phospholipids, zinc to copper and fatty acids in the present specification claims correspond to those defined in the text as follows:

1) page 8, line 22 states that the "ratio of (phosphatidylcholine and/or phosphatidylethanolamine) to (phosphatidylserine and/or phosphatidylinositol) is 0.5 - 20 (wt/wt)". The ratio (PC and/or PE) to (PS and/or PI) is defined as (PC and/or PE) wt/wt units, which is understood to be short for (PC and/or PE) weight units per 1 weight unit of (PS and/or PI);

2) page 7, line 24 reads, "...a ratio of Ω-3 fatty acids to Ω-6 fatty acids of about 2.5 to 5.5 wt/wt". This corresponds to 2.5 to 5.5 weight units Ω-3 fatty acids per 1 weight unit Ω-6 fatty acids; and

3) page 10, line 3 states, "the weight ratio of zinc to copper is between 5 to 12". As it is mentioned that the ratio is between those numbers, it is believed to be clear that it should not be read as a specific ratio of 5:12.

Thus, in view of the above, applicants request that the new matter rejection be withdrawn.

Claims 42-58 were rejected under 35 USC §112, first paragraph, for allegedly not satisfying the enablement

requirement. Applicants believe the present amendment obviates this rejection.

As noted above, claims 42-58 have been amended to recite a method for the treatment of unipolar depression or depression-related disorders, or the prevention of unipolar depression in a person suffering from psychosis, disturbance of personality, loss of a relative, hormonal changes, and neurological disorders. Thus, the claims have been amended so that the individuals that are at a higher risk of developing depression are now further characterized. In the groups that have been further characterized, the prevention of depression due to supplementation is expected to be most effective. Indeed, the Official Action does not contend otherwise.

At this time, the Examiner is respectfully reminded that it is a well-founded principle that any assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reason substantiating the doubts so expressed. As a matter of law, the express teaching of the patent specification cannot be contrary by mere speculation and unsupported assertions on the part of the Patent Office as stated by the Court of Customs and Patent Appeals in the case of *In re Dinh-Nguyen and Stanhagen*, 181 USPQ 46 (CCPA 1974):

> Any assertion by the Patent Office that the enabling disclosure is not commensurate in scope of the protection sought must be supported by evidence or

reason substantiating the doubts so expressed 181 USPQ at 47.

Such a standard must be applied with great care when the conjecture of the Patent Office is contrary to teachings of the specification. When reviewing the position of the Patent Office on this point, it is apparent that no evidence is adduced that is in any way inconsistent with the teaching of the specification.

The Examiner's attention is also respectfully directed to claims 59 and 60, wherein independent claim 59 recites a method for the treatment of depression or depression-related disorders in a person suffering from or at risk of suffering from said depression or depression-related disorders. Claim 60 is dependent on claim 59. Thus, claims 59 and 60 are directed to the treatment of depression and depression-related disorders.

Thus, in view of the above, applicants believe that claims 42-60 are enabled by the present disclosure.

Claims 42-48 and 51-58 were rejected under 35 USC §103(a) as allegedly being unpatentable over HORROBIN, FUGH-BERMAN, MAGGIONI and GROWDON et al. This rejection is respectfully traversed. The claimed invention relates to a composition for the treatment of depression and/or anxiety. The composition may contain natural antioxidants, compositions of the essential fatty acids, and essential nutrients.

However, HORROBIN fails to disclose or suggest the use of the phospholipids recited in the claims for the prevention and/or treatment of depression or depression-related disorders. Indeed, HORROBIN only refers to phospholipids as a possible carrier for the fatty acid DHA.

Moreover, HORROBIN does not teach or mention a mixture of phospholipids comprising phosphatidylcholine and phosphatidylethanolamine and at least one of phosphatidylserine and phosphatidylinositol, wherein the phospholipids are in a ratio of phosphatidylcholine and phosphatidylethanolamine to phosphatidylserine and phosphatidylinositol of 0.5-20:1 (wt/wt).

In an effort to remedy the deficiencies of HORROBIN, the outstanding Official Action cites to MAGGIONI, FUGH-BERMAN and GROWDON et al. Applicants believe that the proposed combination of publications fails to disclose or suggest the claimed invention.

The Official Action states that MAGGIONI discloses the used of phosphatidylserine for treating depression. As to FUGH-BERMAN, the Official Action states that FUGH-BERMAN discloses the use St. John's Wort, hypericine, ginkgo biloba, vitamin B12, folate, SAMe and tryptophan to alleviate depression.

However, while MAGGIONI may disclose the use of phosphatidylserine in treating depressive disorders, MAGGIONI does not teach the use of the additional claimed phospholipids or the claimed ratio of components recited in the claims. Likewise,

FUGH-BERMAN does not teach the use of the additional claimed phospholipids or the claimed amounts and ratios recited in the claims. Thus, applicants believe that FUGH-BERMAN and MAGGIONI fail to remedy the deficiencies of HORROBIN.

As to GROWDON et al., applicants do not believed that the GROWDON et al. publication is directed to a method for treating depression. Instead, it is related to the use of lecithin in situations associated with inadequate cholinergic transmission such as a manic-depressive state. Although this is a mood disorder, it should not be confused with depression.

This is evidenced by the diagnostic handbook DSM-IV for psychiatry on the website http://www.psychnet-uk.com/dsm_iv/major_depression.htm (paper copy enclosed,) wherein the authors mention that severe depressions having a history of elevated, expansive or euphoric mood are excluded from a major depression diagnosis, and are diagnosed as bipolar disorders, i.e. manic depressions, instead. Whereas unipolar depression is characterized by prolonged periods of abnormally lowered mood, a manic-depressive or bipolar disorder is characterized by extreme changes in mood, switching from depressive-like states to extreme euphoria.

The treatment of both disorders is very different. Indeed, standard antidepressants are not effective in the treatment of manic-depressive disorders. Manic depression is normally treated with mood-stabilizers, like carbamazepine, valproate, or lithium. The latter treatment may affect

neurotransmitters like gamma-amino-butyric acid (GABA) and acetylcholine, while antidepressant therapy is aimed at neurotransmitters like serotonin and noradrenalin.

Thus, we believe that one skilled in the art would not combine GROWDON et al. with any of the other cited documents to treat unipolar depression as set forth in the claimed invention.

Applicants also traverse the contention that the ratio of ω-3 to ω-6 fatty acids according to claim 55 would result from routine experimentation of a person skilled in the art. As the Official Action acknowledges, the references do not teach the specific amounts of ratios as claimed. As a result, one of ordinary skill in the art would lack the motivation to combine and modify the above-identified publications in a manner to obtan the claimed invention.

The Examiner is also respectfully reminded that a particular parameter must first be recognized as a result-effective variable, i.e., a variable which uses a recognized result, before the determination of the optimum or workable ranges of the variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). As none of the cited publications teach or characterize the claimed amounts and/or ratios as capable of being optimized, applicants believe that one of ordinary skill in the art would have lacked the motivation to combine each of the claimed components in their recited amounts and ratios. Indeed, none of

the publications even refer to or teach that the claimed components can be placed together in a ratio as claimed that would be beneficial for the prevention and/or treatment of depression or depression-related disorders.

In further support of the present claims, applicants also submit data showing that the combination of the invention is unexpectedly effective for the treatment of depression and its related disorders (Annexes I and II). The data show that the claimed combination of fatty acids, phospholipids and methionine metabolism factors (Supplement I of Annex II) is better than a diet of fatty acids (control diet of Annex II), a diet of vitamins and fatty acids (control diet of Annex I), and a diet of vitamins and fatty acids supplemented with w-3 fatty acids DHA and EPA (Supplement II of Annex I).

From Table 1 in Annex II, it is believed to be apparent that the supplement comprising the claimed combination provides an improved antidepressant effect. This is further confirmed from a comparison of the graphs of Annexes I and II, wherein animals treated with the supplement according to Annex II show less hyperactivity, and thus reduced depression than in any other case.

Furthermore, while the Official Action states that it would be a mater of routine practice to include citrate in the composition,the co-administration of citrate is to establish sufficient amounts of ATP and reducing equivalents in the form of

NADPH available in the cytosol of vascular endothelial cells simultaneously (see page 11, lines 11-27). Thus, citrate plays an important role in treating vascular disorders and depression in accordance with the invention.

A person skilled in the art, knowing about the antioxidant action of citrate (e.g., U.S. 5,234,702 and U.S. 5,077,069 cited on page 5 of the specification), would not be motivated or directed to use the daily dose of citrate according claims 44, 54, or 56.

Finally, the Examiner mentions that the administration of vitamin D3 (see claims 53 and 57) for the purpose of the invention would be obvious over HORROBIN. However, HORROBIN only briefly mentions the use of vitamin D in a general context that covers all vitamins and essential minerals (Example 3). There is no teaching to that directs one skilled in the art ot specifically administer vitamin D3.

Thus, applicant believe that a method for treating unipolar depression comprising the administration of fatty acids, phospholipids and a methionine metabolism factor, let alone in the present ratios or in co-administration with citrate and/or vitamin D3, is not disclosed nor suggest by any of the publications, alone or in combination with each other.

Thus, in view of the above, applicants believe that the proposed combination of HORROBIN, FUGH-BERMAN, MAGGIONI and GROWDON et al. fails to render obvious the claimed invention.

Claim 49 was rejected under 35 USC §103(a) as allegedly being unpatentable over HORROBIN, GROWDON et al. and POLLACK et al. Claim 50 was rejected under 35 USC §103(a) as allegedly being unpatentable over HORROBIN, GROWDON et al. and TAKEDA. These rejections are respectfully traversed.

As noted above, applicants believe that one of ordinary skill in the art would lack the motivation to combine HORROBIN with GROWDON et al. As to POLLACK et al., POLLACK et al. is directed to a composition for treating physiological disorders pertaining to the regulation of the neurotransmitter serotonin. However, applicants respectfully submit that POLLACK et al. fail to teach a method for treating depression by administering to a patient in need thereof a composition containing the claimed components, amounts and ratios. Indeed, POLLACK et al. fail to disclose or suggest a method for treating depression by administering to a patient in need thereof a composition comprising the claimed chain of polyunsaturated fatty acids, the claimed phospholipids and the claimed related compound.

Thus, applicants believe that POLLACK et al. fail to remedy the deficiencies of HORROBIN and GROWDON et al.

TAKEDA teaches a depressive symptom improvement agent. The agent contains carnitine and vitamin B1. The composition relates to an agent designed to provide a stimulant affect to one suffering from depression related stress and fatigue. The TAKEDA publication does not teach the claimed components, amounts or

ratios. As a result, it is believed that the TAKEDA publication fails to remedy the deficiencies of HORROBIN and GROWDON et al.

Thus, in view of the above, applicants request that the rejections be withdrawn.

In view of the foregoing remarks and the present amendment, therefore, applicants believe that the present application is in condition for allowance at the time of the next Official Action, with claims 42-60, as presented. Allowance and passage to issue on that basis is respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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Appendix:

The Appendix includes the following items:

- Annex I: Supplementation of Omega-3 PUFAS does not affect Behavioural Changes Induced by the Olfactory Bulbectomy Model of Depression

- Annex II: The Effects of a Dietary Supplement on Behavioural Changes Induced by the Olfactory Bulbectomy Model of Depression

- Disorder Information Sheet, http://www.psychnet-uk.com/dsm_iv/major_depression.htm

ANNEX I: SUPPLEMENTATION OF OMEGA-3 PUFAS DOES NOT AFFECT BEHAVIOURAL CHANGES INDUCED BY THE OLFACTORY BULBECTOMY MODEL OF DEPRESSION.

Introduction

The olfactory bulbectomized (OBX) rat has been proposed as an animal model of depression [Kelly et al (1997) The olfactory bulbectomized rat as a model of depression: an update. *Pharmacol Ther* 74:299-316]. Following bilateral olfactory bulbectomy, a number of behavioural changes has been observed, including hyperactivity in the open field and deficits in memory in several maze procedures. Typically, behavioural changes induced by OBX are attenuated by chronic (but not acute) antidepressant treatment.

The most commonly employed behavioural indicator of antidepressant activity is attenuation of the OBX-related hyperactivity in the open field. In the present experiment, we investigated the effects of a dietary supplementation of the omega-3 polyunsaturated fatty acids (PUFAs) DHA and EPA on activity changes induced by the OBX model of depression.

Materials and methods

Animals

Twenty-four male Sprague Dawley rats (Harlan, The Netherlands) were 8 weeks old at the start of the experiment and were housed in groups of 4 rats per cage. Rats were housed at controlled room temperature (21 ± 2 °C) and relative humidity of 60 ± 10% under reversed 12 h light – 12 h dark cycle conditions (lights on at 19:00). Tap water and food were freely available throughout the experiment. Starting one day after surgery, standard rodent food (Special Diet Services, Witham, Essex, UK) was replaced by either a control diet or a supplement diet (Table 1). All experiments were carried out with the approval of the Animal Ethics Committee of the Faculties of Pharmacy, Chemistry and Biology of Utrecht University.

Olfactory bulbectomy

After a 4-week acclimatization period, two rats per cage underwent surgery to produce bilateral olfactory bulbectomy and two rats per cage underwent sham surgery. Rats were anaesthetised with Hypnorm (0.7 ml/kg, s.c.) and Dormicum (0.5 ml/kg, s.c.) and two burr holes (2 mm diameter) were drilled in the skull, at 8 mm anterior to bregma, on either side 2 mm from the midline of the frontal bone overlying the olfactory bulbs. The olfactory bulbs were first damaged with the drill and were then aspirated by means of a blunt hypodermic needle attached to a water pump. Prevention of blood loss from the burr holes was achieved by filling them with haemostatic sponge. Sham-operated rats were treated similarly, except that the olfactory bulbs were neither damaged nor removed. One sham-operated animal did not survive surgery.

Diet compositions

The control diet was based on the composition of a standard rodent food. For the supplement diet, part of the soy bean oil was replaced by omega-3 PUFA-rich fish oil. A detailed description of the compositions of the control diet and the supplement diet are provided in Table 1. Both diets were stored in sealed plastic bags at -20 °C until use.

Locomotor activity

Spontaneous locomotor activity was measured both one week before surgery and three weeks after surgery. To this end, rats were individually placed in the centre of a square open field arena (75 × 75 × 50 cm) made of dark grey plastic, and locomotor activity was monitored for 30 min using an automated video tracking system for behavioural registration and analysis (Ethovision, Noldus, Wageningen, The Netherlands).

Table 1: Compositions of the control diet and the supplement diet that were used in the present study.

	Component	Control g/100 g	Supplement g/100g
Oil	Soybean oil	5	2.84
	Marinol C45 .4%		2.16
Proteins	Acid Casein	20	20
	DL-Methionine	0.2	0.2
Carbohydrates	Corn starch	10	10
	Cerelose	52.95	52.95
	Cellulose	5	5
Minerals	CaHPO4*2H2O	1.3	1.3
	CaCO3	1	1
	KH2PO4	0.7	0.7
	KCl	0.7	0.7
	NaCl	0.3	0.3
	MgSO4*7H2O	0.4	0.4
	MgO	0.2	0.2
	Inositol	0.05	0.05
Vitamins	Vitamin mix	1.2	1.2
Minerals	Mineral premix	1	1
Total		100	100

Results

The effects of OBX on spontaneous locomotor activity in rats fed with either the control diet or the supplement diet, are shown in figure 1. Data obtained after surgery are expressed as percentage of control scores. A two-way univariate analysis of variance with the between-subject factors Surgery (Sham or OBX) and Diet (Control or Supplement) revealed a main effect of the factor Surgery [$F(1,19)=12.07$, $p<0.005$], indicating that OBX rats showed an increase in locomotor activity. However, there was no significant effect of Diet, nor a significant Surgery × Diet interaction [both $p>0.60$]. These data show that the consumption of the supplement diet for 3 weeks, does not attenuate the

behavioural changes induced by the OBX model of depression, indicating that the supplement diet has little antidepressant potential.

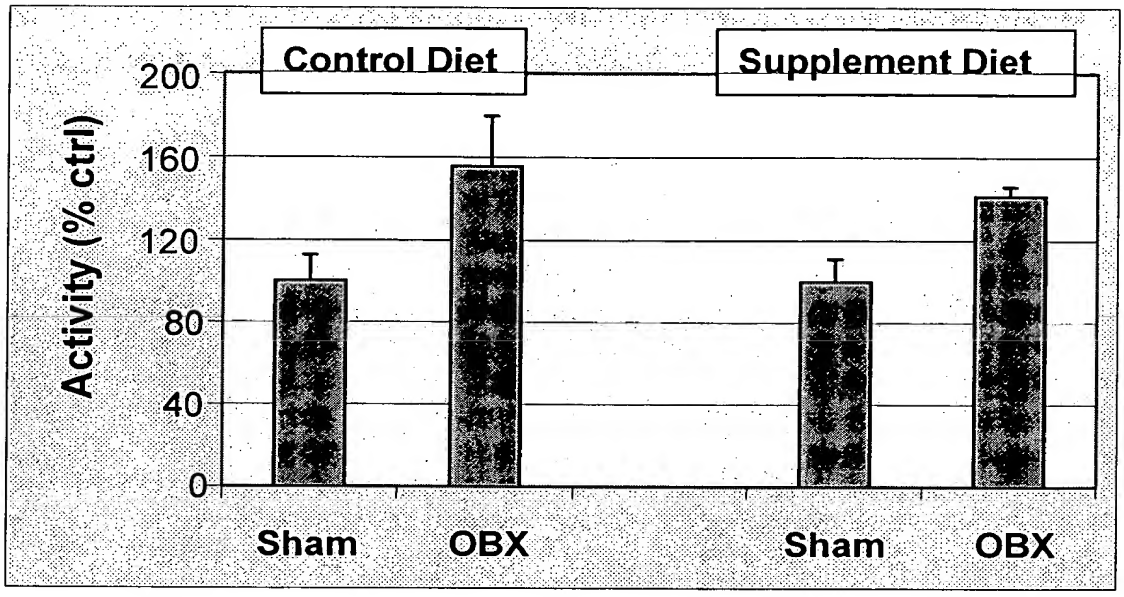

Figure 1: Effects of dietary omega-3 PUFA (DHA and EPA) supplementation on activity changes induced by olfactory bulbectomy (OBX), a rat model of depression. The increase in locomotor activity that is normally observed after OBX, is present in both diet groups, indicating that the PUFA-enrichment in the supplement diet by itself is insufficient to induce an antidepressant-like effect in the OBX model.

ANNEX II: THE EFFECTS OF A DIETARY SUPPLEMENT ON BEHAVIORAL CHANGES INDUCED BY THE OLFACTORY BULBECTOMY MODEL OF DEPRESSION.

Introduction

The olfactory bulbectomized (OBX) rat has been proposed as an animal model of depression [Kelly et al (1997) The olfactory bulbectomized rat as a model of depression: an update. *Pharmacol Ther* 74:299-316]. Following bilateral olfactory bulbectomy, a number of behavioral changes has been observed, including hyperactivity in the open field and deficits in memory in several maze procedures. Typically, behavioral changes induced by OBX are attenuated by chronic (but not acute) antidepressant treatment.

The most commonly employed behavioral indicator of antidepressant activity is attenuation of the OBX-related hyperactivity in the open field. In the present experiment, we investigated the effects of a dietary supplement on activity changes induced by the OBX model of depression.

Materials and methods

Animals

Thirty-two male Sprague Dawley rats (Harlan, The Netherlands) were 8 weeks old at the start of the experiment and were housed in groups of 4 rats per cage. Rats were housed at controlled room temperature (21 ± 2 °C) and relative humidity of 60 ± 10% under reversed 12 h light – 12 h dark cycle conditions (lights on at 19:00). Tap water and food were freely available throughout the experiment. Starting one day after surgery, standard rodent food (Special Diet Services, Witham, Essex, UK) was replaced by either a control diet or a supplement diet (Table 1). All experiments were carried out with the approval of the Animal Ethics Committee of the Faculties of Pharmacy, Chemistry and Biology of Utrecht University.

Olfactory bulbectomy

After a 4-week acclimatization period, two rats per cage underwent surgery to produce bilateral olfactory bulbectomy and two rats per cage underwent sham surgery. Rats were anaesthetized with Hypnorm (0.7 ml/kg, s.c.) and Dormicum (0.5 ml/kg, s.c.) and two burr holes (2 mm diameter) were drilled in the skull, at 8 mm anterior to bregma, on either side 2 mm from the midline of the frontal bone overlying the olfactory bulbs. The olfactory bulbs were first damaged with the drill and were then aspirated by means of a blunt hypodermic needle attached to a water pump. Prevention of blood loss from the burr holes was achieved by filling them with haemostatic sponge. Sham-operated rats were treated similarly, except that the olfactory bulbs were neither damaged nor removed. Two OBX rats did not survive surgery.

Diet compositions

The control diet was based on the composition of a standard rodent food. To the supplement diet, several food components were added, including DHA, EPA, phosphatidylserine, folic acid, Se, Cu, Mg, Zn, and vitamins B6, B12, D3 and E. A detailed description of the compositions of the control diet and the supplement diet are provided in Table 1. Both diets were stored in sealed plastic bags at -20 °C until use. The average intake per animal is of about 20g per day of food.

Locomotor activity

Spontaneous locomotor activity was measured both one week before surgery and three weeks after surgery. To this end, rats were individually placed in the centre of a square open field arena (75 × 75 × 50 cm) made of dark grey plastic, and locomotor activity was monitored for 30 min using an automated video tracking system for behavioral registration and analysis (Ethovision, Noldus, Wageningen, The Netherlands).

Table 1: Compositions of the control diet and the supplement diet that were used in the present study.

	Component	Control g/100 g	Supplement g/100g
Oil*	Soybean oil	5	2.84
	Marinol C45 .4%		2.16
Proteins	Acid Casein	20	20
	DL-Methionine	0.2	0.2
Carbohydrates	Corn starch	10	10
	Cerelose	52.95	50.70
	Cellulose	5	5
Minerals	$CaHPO_4*2H_2O$	1.3	1.3
	$CaCO_3$	1	1
	KH_2PO_4	0.7	0.7
	KCl	0.7	0.7
	NaCl	0.3	0.3
	$MgSO_4*7H_2O$	0.4	0.8
	MgO	0.2	0.4
	Inositol	0.05	0.05
Vitamins	Vitamin mix	1.2	1.2
Minerals	Mineral premix	1	1
Extras	Phosphatidyl serine** (Leci-PS_20P)		1.11
	Vitamine B6		0.0054
	Vitamine B12		0.02
	Foliumzuur		0.0004
	Vitamine E		0.5
	Vitamine D3		0.0004
	Na_2SeO_3*5aq		6.66E-05
	$ZnSO_4*aq$		0.006587
	$CuSO_4*5aq$		0.003145
Total		100	100

*oil comprises both ω-3 fatty acids and ω-6 fatty acids

**phosphatidyl serine (PS) comes from Leci-PS_20P which is a lecithin comprising 18-24% PS, min. 15% phosphatidyl choline (PC), max.
18% phosphatidyl ethanolamine (PE) and max. 10% phosphatidyl inositol (PI).

Results

The effects of OBX on spontaneous locomotor activity in rats fed with either the control diet or the supplement diet are shown in figure 1. Data obtained after surgery are expressed as percentage of preoperative scores. A two-way univariate analysis of variance with the between-subject factors Surgery (Sham or OBX) and Diet (Control or Supplement) revealed a main effect of the factor Surgery [$F(1,26)=6.51$, $p<0.02$], indicating that OBX rats showed an increase in locomotor activity. In addition, a Surgery × Diet interaction [$F(1,26)=4.78$, $p<0.05$] and post-hoc comparisons indicated that the increase in activity was present in the OBX rats fed with the control diet, but not in the OBX rats fed with the supplement diet, as compared to the respective Sham-operated groups. These data show that the consumption of the supplement diet for 3 weeks, attenuates the behavioral changes induced by the OBX model of depression, indicating that the supplement diet has antidepressant potential.

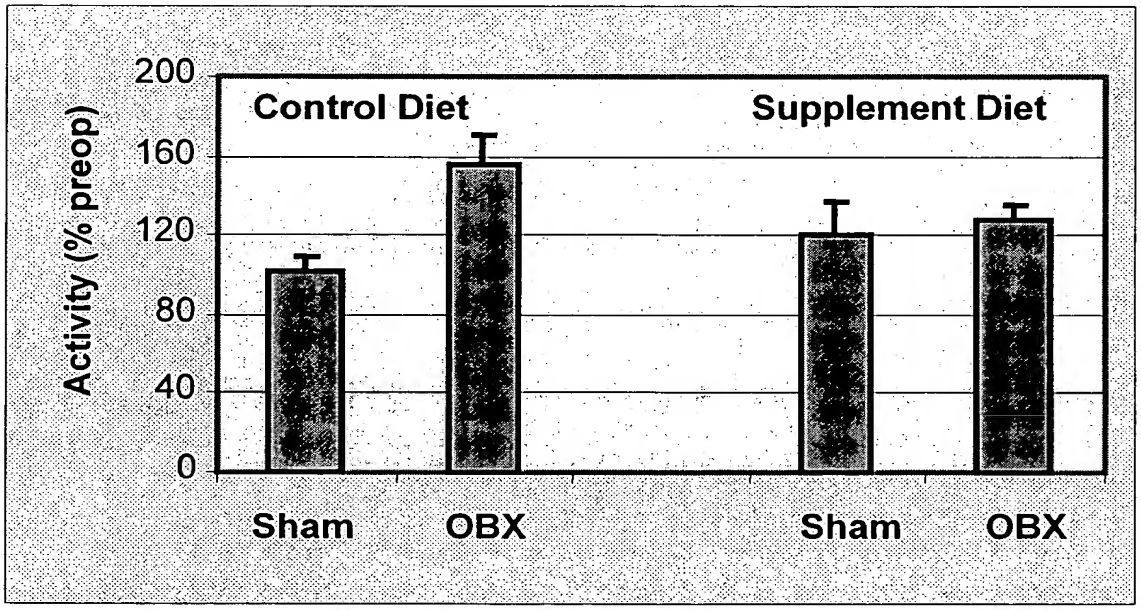

Figure 1: Effects of dietary supplement on activity changes induced by olfactory bulbectomy (OBX), a rat model of depression. The increase in locomotor activity that is normally observed after OBX, is present in the control diet groups, but not in the supplement diet groups. To the supplement diet, several food components were added, including DHA, EPA, phosphatidylserine, folic acid, Se, Cu, Mg, Zn, and vitamins B6, B12, D3 and E.

Disorder Information Sheet

Major Depressive Episode

Depression, which affects people of all ages, income, race, and cultures, is a disturbance of mood and is characterized by a loss of interest or pleasure in normal everyday activities. People who are depressed may feel "down in the dumps" for weeks, months, or even years at a time.

- in the same 2 weeks, the patient has had 5 or more of the following symptoms, which are a definite change from usual functioning. Either depressed mood or decreased interest or pleasure must be one of the five:

  Mood. For most of nearly every day, the patient reports depressed mood or appears depressed to others.

  Interests. For most of nearly every day, interest or pleasure is markedly decreased in nearly all activities (noted by the patient or by others).

  Eating and weight. Although not dieting, there is a marked loss or gain of weight (such as five percent in one month) or appetite is markedly decreased or increased nearly every day.

  Sleep. Nearly every day the patient sleeps excessively or not enough.

  Motor activity. Nearly every day others can see that the patient's activity is agitated or retarded.

  Fatigue. Nearly every day there is fatigue or loss of energy.

  Self-worth. Nearly every day the patient feels worthless or inappropriately guilty. These feelings are not just about being sick; they may be delusional.

  Concentration. Noted by the patient or by others, nearly every day the patient is indecisive or has trouble thinking or concentrating.

  Death. The patient has had repeated thoughts about death (other than the fear of dying), suicide (with or without a plan) or has made a suicide attempt.

- These symptoms cause clinically important distress or impair work, social or personal functioning.

- They don't fulfill criteria for Mixed Episode

- This disorder is not directly caused by a general medical condition or the use of substances, including prescription

medications.

Unless the symptoms are severe (defined as severely impaired functioning, severe preoccupation with worthlessness, ideas of suicide, delusions or hallucinations or psychomotor retardation), the episode has not begun within two months of the loss of a loved one.

Use the following codes (including Chronic) for the current or most recent Major Depressive Episode in Major Depressive, Bipolar I or Bipolar II Disorders.

Fifth Digit Severity Code for Major Depressive Episode.

.1 Mild. Symptoms barely meet criteria for major depression and result in little distress or interference with the patient's ability to work, study or socialize.

.2 Moderate. Intermediate between Mild and Severe.

.3 Severe without Psychotic Features. The number of symptoms well exceeds the minimum for diagnosis, and they markedly interfere with patient's work, social or personal functioning.

.4 With Psychotic Features. The patient has delusions or hallucinations, which may be mood-congruent or mood-incongruent. Specify, if possible:

> Severe With Mood-congruent Psychotic Features. The content of the patient's delusions or hallucinations is completely consistent with the typical themes of depression: death, disease, guilt, nihilism, personal inadequacy or punishment that is deserved.
>
> Severe With Mood-incongruent Psychotic Features. The content of the patient's delusions or hallucinations is not consistent with the typical themes of depression. Mood incongruent themes include delusions of control, persecution, thought broadcasting and thought insertion.

.5 In Partial Remission. Use this code for patients who formerly met full criteria for Major Depressive Episode and now either (1) have fewer than five symptoms or (2) have had no symptoms for less than two months.

.6 In Full Remission. The patient has had no material evidence of Major Depressive Episode during the past 2 months.

.0 Unspecified.

Chronicity Specifier: Chronic. All the criteria for a Major Depressive Episode have been met without interruption for the previous 2 years or longer.

Psychomotor Agitation and Psychomotor Retardation

Psychomotor agitation and retardation occur in depression, producing states of over activity and under activity respectively. Agitation and retardation can lead to impaired cognition, judgment, reason, and decision making, which often further isolates depressed people and prolongs symptoms. Psychomotor agitation can also lead to generalized restlessness.

Motor agitation is rarer than motor retardation and is often occurs in the elderly. Over activity in this sense does not mean mania. The agitated state in major depressive disorder should not be confused with the manic episode that occurs in bipolar disorder, when mood is temporarily elevated by a transient sense of hope and elation.

Psychomotor activities are the physical gestures that result from mental processes and are a product of the psyche. Many psychomotor behaviors associated with mental disorder affect impulses, cravings, instincts, and wishes. The spectrum of agitated behavior includes the following:

Incoherent conversation
Expansive gesturing
Pacing and hair twirling

Psychomotor retardation manifests as a slowing of coordination, speech, and impaired articulation. In this state, a person appears sluggish and seems hesitant or confused in speech and intention.

Essentially Features:

Physical illness, alcohol, medication, or street drug use.
Normal bereavement.
Bipolar Disorder
Mood-incongruent psychosis (e.g., Schizoaffective Disorder, Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified).

Major Depressive Disorder causes the following mood symptoms:

- Abnormal depressed mood:

Sadness is usually a normal reaction to loss. However, in Major Depressive Disorder, sadness is abnormal because it:

Persists continuously for at least 2 weeks.

Causes marked functional impairment.

Causes disabling physical symptoms (e.g., disturbances in sleep, appetite, weight, energy, and psychomotor activity).

Causes disabling psychological symptoms

(e.g., apathy, morbid preoccupation with worthlessness, suicidal ideation, or psychotic symptoms).

The sadness in this disorder is often described as a depressed, hopeless, discouraged, "down in the dumps," "blah," or empty. This sadness may be denied at first. Many complain of bodily aches and pains, rather than admitting to their true feelings of sadness.

- Abnormal loss of interest and pleasure mood:

The loss of interest and pleasure in this disorder is a reduced capacity to experience pleasure which in its most extreme form is called anhedonia.

The resulting lack of motivation can be quite crippling.

- Abnormal irritable mood:

This disorder may present primarily with irritable, rather than depressed or apathetic mood. This is not officially recognized yet for adults, but it is recognized for children and adolescents.

Unfortunately, irritable depressed individuals often alienate their loved ones with their cranky mood and constant criticisms.

- Major Depressive Disorder causes the following physical symptoms:

Abnormal appetite: Most depressed patients experience loss of appetite and weight loss. The opposite, excessive eating and weight gain, occurs in a minority of depressed patients. Changes in weight can be significant.

Abnormal sleep: Most depressed patients experience difficulty falling asleep, frequent awakenings during the night or very early morning awakening. The opposite, excessive sleeping, occurs in a minority of depressed patients.

Fatigue or loss of energy: Profound fatigue and lack of energy usually is very prominent and disabling.

Agitation or slowing: Psychomotor retardation (an actual physical slowing of speech, movement and thinking) or psychomotor agitation (observable pacing and physical restlessness) often are present in severe Major Depressive Disorder.

- Major Depressive Disorder causes the following cognitive symptoms:

  Abnormal self-reproach or inappropriate guilt:

  This disorder usually causes a marked lowering of self-esteem and self-confidence with increased thoughts of pessimism, hopelessness, and helplessness. In the extreme, the person may feel excessively and unreasonably guilty.

  The "negative thinking" caused by depression can become extremely dangerous as it can eventually lead to extremely self-defeating or suicidal behavior.

  Abnormal poor concentration or indecisiveness:

  Poor concentration is often an early symptom of this disorder. The depressed person quickly becomes mentally fatigued when asked to read, study, or solve complicated problems.

  Marked forgetfulness often accompanies this disorder. As it worsens, this memory loss can be easily mistaken for early senility (dementia).

- Abnormal morbid thoughts of death (not just fear of dying) or suicide:

  The symptom most highly correlated with suicidal behavior in depression is hopelessness

Associated Features and Comorbitity

Anxiety:

80 to 90% of individuals with Major Depressive Disorder also have anxiety symptoms (e.g., anxiety, obsessive preoccupations, panic attacks, phobias, and excessive health concerns).

Separation Anxiety may be prominent in children.

About one third of individuals with Major Depressive Disorder also have a full-blown anxiety disorder (usually either Panic Disorder, Obsessive-Compulsive Disorder, or Social Phobia).

Anxiety in a person with major depression leads to a poorer response to treatment, poorer

social and work function, greater likelihood of chronicity and an increased risk of suicidal behavior.

Eating Disorders:

Individuals with Anorexia Nervosa and Bulimia Nervosa often develop Major Depressive Disorder.

Psychosis:

Mood congruent delusions or hallucinations may accompany severe Major Depressive Disorder.

Substance Abuse:

The combination of Major Depressive Disorder and substance abuse is common (especially Alcohol and Cocaine).

Alcohol or street drugs are often mistakenly used as a remedy for depression. However, this abuse of alcohol or street drugs actually worsens Major Depressive Disorder.

Depression may also be a consequence of drug or alcohol withdrawal and is commonly seen after cocaine and amphetamine use.

Medical Illness:

25% of individuals with severe, chronic medical illness (e.g., diabetes, myocardial infarction, carcinomas, stroke) develop depression.

About 5% of individuals initially diagnosed as having Major Depressive Disorder subsequently are found to have another medical illness which was the cause of their depression.

Medical conditions often causing depression are:

Endocrine disorders: hypothyroidism, hyperparathyroidism, Cushing's disease, and diabetes mellitus.

Neurological disorders: multiple sclerosis, Parkinson's Disease, migraine, various forms of epilepsy, encephalitis, brain tumors.

Medications: many medications

can cause depression, especially antihypertensive agents such as calcium channel blockers, beta blockers, analgesics and some anti-migraine medications.

Mortality: Up to 15% of patients with severe Major Depressive Disorder die by suicide. Over age 55, there is a fourfold increase in death rate.

Premorbid History: 10-25% of patients with Major Depressive Disorder have preexisting Dysthymic Disorder. These "double depressions" (i.e., Dysthymia + Major Depressive Disorder) have a poorer prognosis.

Gender: Males and females are equally affected by Major Depressive Disorder prior to puberty. After puberty, this disorder is twice as common in females as in males. The highest rates for this disorder are in the 25- to 44-year-old age group.

Prevalence: The lifetime risk for Major Depressive Disorder is 10% to 25% for women and from 5% to 12% for men. At any point in time, 5% to 9% of women and 2% to 3% of men suffer from this disorder. Prevalence is unrelated to ethnicity, education, income, or marital status.

Onset: Average age at onset is 25, but this disorder may begin at any age.

Psychological stress: Stress appears to play a prominent role in triggering the first 1-2 episodes of this disorder, but not in subsequent episodes.

Duration: An average episode lasts about 9 months.

Course: Course is variable. Some people have isolated episodes that are separated by many years, whereas others have clusters of episodes, and still others have increasingly frequent episodes as they grow older. About 20% of individuals with this disorder have a chronic course.

Recurrence: The risk of recurrence is about 70% at 5 year follow up and at least 80% at 8 year follow-up. After the first episode of Major Depressive Disorder, there is a 50%-60% chance of having a second episode, and a 5-10% chance of having a Manic Episode (i.e., developing Bipolar I Disorder). After the second episode, there is a 70% chance of having a third. After the third episode, there a 90% chance of having a fourth.
The greater number of previous episodes is an important risk factor for recurrence.

Recovery: For patients with severe Major Depressive Disorder, 76% on antidepressant therapy recover, whereas only 18% on placebo recover. For these severely depressed patients, significantly more recover on antidepressant therapy than on interpersonal psychotherapy. For these same patients, cognitive therapy has been shown to be no more effective than placebo.

New research shows that a medication/psychotherapy combination - preferably Cognitive Behavior Therapy - seems to be most effective.

Poor Outcome: Poor outcome or chronicity in Major Depressive Disorder is associated with the following:

Inadequate treatment

Severe initial symptoms

Early age of onset

Greater number of previous episodes

Only partial recovery after one year

Having another severe mental disorder (e.g. Alcohol Dependency, Cocaine Dependency)

Severe chronic medical illness

Family dysfunction

Familial Pattern And Genetics: There is strong evidence that major depression is, in part, a genetic disorder:

Individuals who have parents or siblings with Major Depressive Disorder have a 1.5-3 times higher risk of developing this disorder.

The concordance for major depression in monozygotic twins is substantially higher than it is in dizygotic twins. However, the concordance in monozygotic twins is in the order of about 50%, suggesting that factors other than genetic factors are also involved.

Children adopted away at birth from biological parents who have a depressive illness carry the same high risk as a child not adopted away, even if they are raised in a family where no depressive illness exists.

Interestingly, families having Major Depressive Disorder have an increased risk of developing Alcoholism and AttentionDeficit/Hyperactivity Disorder.

Differential Diagnosis

Some disorders display similar or sometimes even the same symptoms. The clinician, therefore, in his diagnostic attempt has to differentiate against the following disorders which he needs to rule out to establish a precise diagnosis.

Exclude depressions due to physical illness, medications, or street drug use:

If due to physical illness, diagnose: Mood Disorder Due to a General Medical Condition.

If due to alcohol, diagnose: Alcohol-Induced Mood Disorder.

If due to other substance use, diagnose: Other Substance-Induced Mood Disorder.

Organic Causes Of Severe Depression:

Illnesses: Organic Mood Syndromes caused by: Acquired Immune Deficiency Syndrome (AIDS), Adrenal (Cushing's or Addison's Diseases), Cancer (especially pancreatic and other GI), Cardiopulmonary disease, Dementias (including Alzheimer's Disease); Epilepsy, Fahr's Syndrome, Huntington's Disease, Hydrocephalus, Hyperaldosteronism, Infections (including HIV and neurosyphilis), Migraines, Mononucleosis, Multiple Sclerosis, Narcolepsy, Neoplasms, Parathyroid Disorders (hyper- and hypo-), Parkinson's Disease, Pneumonia (viral and bacterial), Porphyria, Postpartum, Premenstrual Syndrome, Progressive Supranuclear Palsy, Rheumatoid Arthritis, Sjogren's Arteritis, Sleep Apnea, Stroke, Systemic Lupus Erythematosus, Temporal Arteritis, Trauma, Thyroid Disorders (hypothyroid and "apathetic" hyperthyroidism), Tuberculosis, Uremia (and other renal diseases), Vitamin Deficiencies (B12, C, folate, niacin, thiamine), Wilson's Disease.

Drugs: Acetazolamine, Alphamethyldopa, Amantadine, Amphetamines, Ampicillin, Azathioprine (AZT), 6-Azauridine, Baclofen, Beta Blockers, Bethanidine, Bleomycin, Bromocriptine, C-Asparaginase, Carbamazepine, Choline, Cimetidine, Clonidine, Clycloserin, Cocaine, Corticosteroids (including ACTH), Cyproheptadine, Danazol, Digitalis, Diphenoxylate, Disulfiram, Ethionamide, Fenfluramine, Griseofulvin, Guanethidine, Hydralazine, Ibuprofen, Indomethacin, Lidocaine, Levodopa, Methoserpidine, Methysergide, Metronidazole, Nalidixic Acid, Neuroleptics (butyrophenones, phenothiazines, oxyindoles), Nitrofurantoin, Opiates, Oral Contraceptives, Phenacetin, Phenytoin, Prazosin, Prednisone, Procainamide, Procyclidine, Quanabenzacetate, Rescinnamine, Reserpine, Sedative/Hypnotics (barbiturates, benzodiazepines, chloral hydrate), Streptomycin, Sulfamethoxazole, Sulfonamides, Tetrabenazine, Tetracycline, Triamcinolone, Trimethoprim, Veratrum, Vincristine.

Exclude depressions having a previous history of elevated, expansive, or euphoric mood:

If previous history of a Manic Episode, diagnose: Bipolar I Disorder.

If previous history of recurrent Major Depressive Episodes and at least one

Hypomanic Episode, diagnose: Bipolar II Disorder.

If previous history of recurrent Hypomanic Episodes and brief, mild depressive episodes (milder than Major Depressive Episodes), diagnose: Cyclothymic Disorder

Exclude depressions that merely represent normal bereavement, instead diagnose: Uncomplicated Bereavement.

Exclude depressions associated with mood-incongruent psychosis:

If previous history of at least 2 weeks of delusions or hallucinations occurring in the absence of prominent mood symptoms, diagnose either: Schizoaffective Disorder, Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.

Exclude mild depressions:

If only mild depression present for most of past 2 years (or 1 year in children), diagnose: Dysthymic Disorder.

If only brief mild depression clearly triggered by stress, diagnose: Adjustment Disorder with Depressed Mood, or Adjustment Disorder with Mixed Anxiety and Depressed Mood.

If mild depression is clinically significant, but does not meet the criteria for any of the previously described disorders, diagnose: Depressive Disorder Not Otherwise Specified.

In the elderly, it is often difficult to distinguish between early dementia or Major Depressive Disorder:

If there is a premorbid history of declining cognitive function in the absence of severe depression, diagnose: Dementia.

If there was a relatively normal premorbid state and somewhat abrupt cognitive decline associated with severe depression, diagnose: Major Depressive Disorder.

Cause:

Changes in the body's chemistry influence mood and thought processes, and biological factors contribute to some cases of depression. In addition, chronic and serious illness such as heart disease or cancer may be accompanied by depression. With many individuals, however, depression signals first and

foremost that certain mental and emotional aspects of a person's life are out of balance.

Significant transitions and major life stressors such as the death of a loved one or the loss of a job can help bring about depression. Other more subtle factors that lead to a loss of identity or self-esteem may also contribute. The causes of depression are not always immediately apparent, so the disorder requires careful evaluation and diagnosis by a trained mental health care professional.

Sometimes the circumstances involved in depression are ones over which an individual has little or no control. At other times, however, depression occurs when people are unable to see that they actually have choices and can bring about change in their lives.

Treatment

Depressive illnesses are highly responsive to treatment. In fact, 80 percent of people with depression report feeling better within a few weeks of starting treatment.

There is still some stigma, or reluctance, associated with seeking help for emotional and mental problems, including depression. Unfortunately, feelings of depression often are viewed as a sign of weakness rather than as a signal that something is out of balance. The fact is that people with depression can not simply 'snap out of it' and feel better spontaneously.

Both psychotherapy and medication may be needed to treat depression. Although medication may help to control it, individuals must learn to recognize their own patterns of depression and develop more effective ways to cope with them. Treatment success depends on factors such as the type of depression, its severity, how long it has been going on, and how an individual responds to treatment. Left untreated, depression can become chronic and even worsen.

Counseling and Psychotherapy [See Therapy Section]:

There are several approaches to psychotherapy – including cognitive-behavioral, interpersonal, psychodynamic and other kinds of 'talk therapy' – that help depressed individuals recover. Psychotherapy offers people the opportunity to identify the factors that contribute to their depression and to deal effectively with the psychological, behavioral, interpersonal and situational causes.

Pharmacotherapy [See Psychopharmacology Section] :

Medication: Most antidepressants believed to be equally effective in equivalent therapeutic doses. Expect a 2- to 6-week latent period before the full effect is seen at therapeutic doses. To prevent relapse, continue medication for at least 4 to 9 months after patient becomes asymptomatic.

Tricyclic Antidepressants (TCAs):

Imipramine.
Nortriptyline .

Second-generation Antidepressants:

Bupropion (Wellbutrin).
V enlafaxine (Effexor).
Trazodone (Desyrel).
Nefazodone (Serzone).
Mirtazapine (Remeron).

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